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Antithrombotic Strategies in Vascular Surgery: Evidence and Practice

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Background. *The aim of this study was to evaluate the current practice of peri and postoperative antithrombotic therapy in vascular surgery in Austria and to compare this with the results of randomised prospective clinical trials.*
Methods. *A questionnaire assessing intra, postoperative and long-term antithrombotic treatment in 13 different surgical procedures (three supra-aortic, three aorto-iliac reconstructions and seven inguinal and infra-inguinal arterial reconstructions) was sent to all 22 institutions training vascular surgical fellows in Austria.*
Results. *Intraoperative antithrombotic therapy was quite consistently performed with unfractionated heparin (UFH) with or without acetylsalicylic acid (ASA). Early and long-term postoperative therapy differed considerably. Most centres used low molecular weight heparin (LMWH) for early postoperative therapy after vascular reconstructions, in >75% combined with ASA and/or clopidogrel. Long-term therapy consisted of antiplatelet agents in all centres. Vascular grafts were anticoagulated with UFH in 25% of the centres in the early postoperative period, the remaining institutions used LMWH± antiplatelet agents. For long-term antithrombotic therapy cumarins were used in 75% of the centres, predominantly for venous grafts. Distal prosthetic grafts were mainly treated with antiplatelet agents. Intraoperative antithrombotic therapy was in accordance to present guidelines, postoperative antithrombotic therapy, however, differed considerably between the participating institutions and the results of available controlled studies.*
Conclusion. *Optimal antithrombotic strategies during and after vascular surgery are still under debate, and current practice often differs from available evidence. Vascular surgical societies should be encouraged to define recommendations on antiplatelet therapy and anticoagulation for different vascular interventions.*

Keywords: Anticoagulation; Antiplatelet agents; Vascular surgery; Graft patency.

Introduction

Antithrombotic therapy is a fundamental component of vascular surgery and contributes significantly to the early and late outcomes of vascular reconstructions. The first anticoagulant substance used intraoperatively was unfractionated heparin (UFH),[1] enabling successful completion of vascular surgical procedures that had previously been associated with high perioperative thrombosis rates. Nowadays, antithrombotic therapy in conventional vascular surgery comprises antiplatelet agents, vitamin K antagonists, thrombin inhibitors, UFH and low molecular weight heparins (LMWH). The intraoperative use of these drugs aims to reduce or preclude thrombosis at the site of surgery and thromboembolic events downstream. Postoperatively, the main aim of antithrombotic therapy is to increase vascular reconstruction and bypass patency rates. Furthermore, antiplatelet agents have been shown to significantly reduce cardiovascular, cerebrovascular and peripheral vascular morbidity and mortality.[2–4]

However, optimal anticoagulation and antiplatelet strategies during and after vascular surgery are still under debate. Although several good controlled studies investigated antithrombotic therapies for surgical interventions in arterial occlusive disease, such therapies may vary with the type of surgery, the use of grafts or stents, and the clinical situation of patients. Therefore, stringent guidelines or even recommendations are rare. The aim of this study was

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to evaluate the current practice of perioperative and postoperative antithrombotic therapy in vascular surgery in Austria for procedures of different vascular regions, and compare it with the results of the existing controlled studies.

Methods

In March 2004, a questionnaire assessing antithrombotic strategies before, during and after vascular surgery was sent to all 22 institutions training vascular surgical fellows in Austria. These centres were selected because of their great expertise in this field and the highly standardised institutional guidelines, which are mandatory for all members of such institutions. Therefore, we assumed that the answers to the questionnaire may best represent the current state of applied evidence in antithrombotic therapy in vascular surgery in most vascular surgical departments in Western Europe.

The questionnaire asked for general antithrombotic strategies for 'standard' patients (without a coexisting thromboembolic risk, stroke, bleeding tendency, the need of individual therapy because of other reasons, or multiple interventions in different vascular region); for therapeutic regimens for pre and intraoperative anticoagulation, early postoperative antithrombotic therapy (from the first day after surgery until discharge from the hospital), and for modality and duration of long-term outpatient antithrombotic therapy. Antithrombotic strategies were assessed for 13 different surgical procedures (three supra aortic, four aorto-iliac and inguinal reconstructions and six types of infra-inguinal bypass surgery).

Results

Of the 22 questionnaires, 16 were returned within 2 months (72%); institutions that did not respond or decided not to participate were not contacted a second time. Intraoperative antithrombotic therapy is shown in Table 1, postoperative modalities on the ward in Table 2, and outpatient anticoagulant practice is shown in Table 3. The intraoperative anticoagulation regimen was quite consistent within the responding institutions and the type of surgery. UFH was given in all institutions as an intravenous bolus prior to arterial clamping. Ten of the responding institutions used 5000 international units (IU) of UFH, one used 30 IU UFH per kg body weight, three used 100 IU UFH per kg body weight, one unit administered 7000–9000 IU UFH and one institution routinely used 10,000 IU UFH for all surgical procedures.

Carotid, vertebral and subclavian artery reconstructions

For intraoperative anticoagulation during carotid endarterectomy, vertebral artery surgery and subclavian artery surgery, nine institutions (56%) used UFH alone, and in seven centres (44%) UFH was combined with ASA and/or clopidogrel. For anticoagulation during the early postoperative period (patients in hospital), LMWH was used in 15 centres (94%) in a prophylactic dose (40 mg enoxaparin once daily subcutaneously), most often combined with antiplatelet drugs. Antiplatelet agents were the preferred treatment for outpatients after supra-aortic artery reconstruction and consisted of ASA alone in 14 institutions (87.5%) and of lifelong clopidogrel and ASA in two institutions (12.5%).

Aorto-iliac and inguinal reconstructions

For antithrombotic therapy during surgical interventions of aorto-iliac disease 14 (87.5%) of all respondents used UHF alone, two (12.5%) respondents used ASA and UFH. Early postoperative therapy consisted of LMWH in all institutions, but was combined with antiplatelet drugs in 11 centres (69%). In one centre (6%) UFH + ASA were given after inguinal endarterectomy. Low dose LMWH (40 mg enoxaparin once daily subcutaneously) was given in 12 responding institutions, the other centres used half of the usual therapeutic dose (1 mg enoxaparin/kg body weight), administered once daily. The outpatient treatment after aorto-iliac surgery consisted of ASA in most centres. Only one institution treated patients with a combination of ASA and clopidogrel, and one refrained from any long-term antiaggregatory treatment after surgery for abdominal aortic aneurysm or aorto-iliac occlusive disease.

Infrainguinal bypass surgery

UFH was used by all centres for intraoperative anticoagulation in all inguinal and infra-inguinal vascular surgical interventions. Three centres (19%) combined UFH with ASA during all kinds of infra-inguinal bypass surgery. Early postoperative anticoagulation varied considerably: for saphenous vein bypass grafts to popliteal (above and below knee) and crural arteries, a minority of centres used UFH alone (four institutions, 25%). UFH was administered as a

Table 1. Intraoperative anticoagulation during vascular surgery

	UFH	UFH + ASA	UFH + ASA + C	UFH + C
Supra-aortic surgery				
Carotid endarterectomy, vertebral artery surgery, subclavia transposition/bypass	9	5	1	1
Aorto-iliac reconstructions				
Infra renal aortic aneurysm	14	2	0	0
Aorto-iliac occlusive disease	14	2	0	0
Common and external iliac occlusion	14	2	0	0
Inguinal endarterectomy ± patch	13	3	0	0
Infrainguinal bypass grafting				
Venous grafts				
Above knee femoropopliteal bypass, below knee femoropopliteal bypass, crural bypass	13	3	0	0
Prosthetic grafts				
Above knee femoropopliteal bypass (PTFE/dacron), below knee femoropopliteal bypass (PTFE), crural bypass (PTFE)	13	3	0	0

Results from the 16 responses to a survey of anticoagulation practice during vascular surgery in Austria. UFH, unfractionated heparin; ASA, acetylsalicylic acid; C, clopidogrel; PTFE, polytetrafluoroethylene.

continuous intravenous infusion, aiming at an aPTT ratio of 2–2.5. Fourteen centres (88%) used LMWH, about half of them in combination with antiaggregatory agents. Prosthetic grafts below the knee were anticoagulated with UFH alone in four centres (25%). Most other centres used LMWH for all kinds of prosthetic bypasses, with a variable rate of additional antiplatelet therapy. LMWH was administered in eight centres (50%) in a prophylactic dose (40 mg enoxaparin once daily subcutaneously), the other half of respondents used a full anticoagulation dose. Long-term outpatient treatment of saphenous vein bypass grafts consisted, depending on the length of bypass, either of vitamin K antagonists alone (8–11 centres; 50–69%) or ASA alone 4–8 centres (25–50%). Only in one centre ASA was combined with clopidogrel. The target INR for patients on vitamin K antagonists was 3–3.5. In contrast, prosthetic bypasses above the knee were treated predominantly with ASA and/or clopidogrel (12 centres; 75%). For below knee prosthetic bypasses,

Table 2. Early postoperative anticoagulation after vascular surgery

	ASA	UFH	UFH + ASA	LMWH	LMWH + ASA	LMWH + ASA + C
Supra-aortic surgery						
Carotid endarterectomy, vertebral artery surgery, subclavia transposition/bypass	1	0	0	3	10	2
Aorto-iliac reconstructions						
Infra renal aortic aneurysm	0	0	0	5	10	1
Aorto-iliac occlusive disease	0	0	0	5	10	1
Common and external iliac occlusion	0	0	0	5	10	1
Inguinal endarterectomy ± patch	0	0	1	4	10	1
Infrainguinal bypass grafting						
Venous grafts						
Above knee femoropopliteal bypass	0	2	0	5	8	1
Below knee femoropopliteal bypass	0	3	0	7	6	0
Crural bypass (vein)	0	4	0	6	6	0
Prosthetic grafts						
Above knee femoropopliteal bypass (PTFE/dacron)	0	2	0	4	8	2
Below knee femoropopliteal bypass (prosthetic)	2	4	0	6	3	1
Crural bypass (PTFE)	1	4	0	5	5	1

Results from the 16 responses to a survey of anticoagulation practice during vascular surgery in Austria. ASA, acetylsalicylic acid; UFH, unfractionated heparin; LMWH, low molecular weight heparin; C, clopidogrel; PTFE, polytetrafluoroethylene.

Table 3. Postoperative outpatient anticoagulation after vascular surgery

	ASA	C	ASA + C	VKA	VKA + ASA	NIL
Supra-aortic surgery						
Carotid endarterectomy, vertebral artery surgery, subclavia transposition/bypass	14	0	2	0	0	0
Aorto-iliac reconstructions						
Infra renal aortic aneurysm	14	0	1	0	0	1
Aorto-iliac occlusive disease	14	0	1	0	0	1
Common and external iliac occlusion	15	0	1	0	0	0
Inguinal endarterectomy ± patch	15	0	1	0	0	0
Infrainguinal bypass grafting						
Venous grafts						
Above knee femoropopliteal bypass	8	0	0	8	0	0
Below knee femoropopliteal bypass	5	0	0	11	0	0
Crural bypass	4	0	1	11	0	0
Prosthetic grafts						
Above knee femoropopliteal bypass (PTFE/dacron)	10	0	2	3	1	0
Below knee femoropopliteal bypass (prosthetic)	7	0	1	7	1	0
Crural bypass (PTFE)	3	1	0	8	4	0

Results from the 16 responses to a survey of anticoagulation practice during vascular surgery in Austria. ASA, acetylsalicylic acid; C, clopidogrel; VKA, vitamin K antagonists; nil, no anticoagulation at all; PTFE, polytetrafluoroethylene.

the majority of institutions used vitamin K antagonists (8–12 centres; 50–75%). The target INR for patients on vitamin K antagonists was 3–3.5.

Discussion

The present survey was conducted in institutions training vascular surgical fellows in Austria. Due to the structure of such departments in Austria and their function as opinion leaders for vascular surgeons in other institutions, treatment policies should best reflect the current state of applied evidence in antithrombotic therapy in Austria and Western Europe. The aim of the study was to asses antithrombotic practice for standard patients. Patients with coexisting conditions requiring individual treatment different from these standards were excluded and are not addressed in the current survey. In the last decade, several randomised, controlled studies for intraoperative and postoperative anticoagulation for arterial reconstructions were conducted and published. Also, large studies with antiplatelet agents for patients with symptomatic atherosclerosis or at risk of ischaemic events, predominantly in the coronary arteries, but also for stroke and peripheral limb ischaemia were published. Low dose ASA has been shown to reduce the risk of occlusive events in all vascular regions.[2,5] Long-term use of clopidogrel compared to ASA in patients with atherosclerotic vascular disease has been demonstrated to be more effective in reducing the combined risk of myocardial infarction, ischaemic stroke and vascular death.[3] However, the absolute risk reduction rate was only 0.5%, indicating that 200 patients need to be treated in order to prevent one ischaemic episode. A combination of clopidogrel and ASA further reduced the risk of recurrent ischaemic events; however, the risk of major bleeding was increased in patients receiving a combination of these drugs.[4]

The data of this survey demonstrate that intraoperative anticoagulation is the least controversial strategy for anticoagulation during vascular surgery. For aorto-iliac disease, inguinal and infra-inguinal revascularization, there is no evidence of the benefit of adjuvant antiplatelet therapy. Therefore, UFH alone is the most commonly applied modality of intraoperative anticoagulation. In carotid artery surgery, initial reports suggested that intraoperative anticoagulation with heparin as well as high dose ASA (600–1200 mg) were associated with a lower risk of perioperative stroke.[6] A large prospective trial, however, has clearly demonstrated that low dose ASA preoperatively was associated with less perioperative neurological events compared to a high dose regimen.[7] A recent randomized trial of ASA and placebo versus ASA and clopidogrel preoperatively reports a reduction of postoperative emboli measured by trans-cranial Doppler.[8] Yet, in the clopidogrel group, haemostasis was significantly prolonged, measured by an increase of time from flow restoration of the internal carotid artery to completion of skin closure.

More recently, a dedicated trial for secondary prevention in patients with ischaemic neurological

deficit comparing clopidogrel and ASA with clopidogrel alone was published.[9] The results of MATCH suggest, that dual therapy does confer a risk reduction regarding the endpoints ischaemic stroke, myocardial infarction, vascular death or rehospitalisation for acute ischaemia. However, reduction in risk was outweighed by life threatening or major bleeding episodes. Nevertheless, the results of the study have evoked some comments,[10,11] indicating caution in banning dual therapy from the list of treatment options for secondary prevention of stroke and recommending a more cautious utilization until further studies are undertaken.[11]

For vertebral and subclavian artery surgery, no trials evaluating the benefit of anticoagulation during surgery are published, however, we suggest that similar regimens to those for carotid endarterectomy are appropriate.

LMWH is widely accepted for prophylaxis of postoperative venous thromboembolism. It has been proven as equally effective and safer compared to UFH.[12] For most interventions, except infrainguinal bypass surgery, LMWH was administered at the dose used for prophylaxis of venous thromboembolism. For infrainguinal bypass-surgery, LMWH was administered in eight centres in a prophylactic dose, the other half of respondents used a full anticoagulation dose. For the most distal bypasses, a continuous infusion of UFH was used by a quarter of the responding institutions. The evidence for this therapeutic modality is not overwhelming. One prospective randomised trial including 201 patients concluded LMWH to be as safe but more effective than UFH for the prevention of graft thrombosis.[13] However, both substances were administered subcutaneously. Therefore, these results are not entirely comparable to an intravenous administration, as the bio-availability of UFH is inferior to LMWH when administered subcutaneously.

The area showing most discrepancy in postoperative out patient treatment is infra-inguinal bypass surgery. Studies comparing oral anticoagulation with vitamin K antagonists versus placebo[14] and antiplatelet agents versus placebo[15] clearly demonstrate the need for adjuvant antithrombotic therapy after bypass surgery. The role of anticoagulation and platelet inhibitors for different bypass materials after infra-inguinal surgery is well documented by several prospective randomised trials and meta-analyses.[16–21] In preventing prosthetic infra-inguinal bypass graft occlusions, low dose ASA is superior to vitamin K antagonists. Oral anticoagulation, on the other hand, does improve long-term patency rates for infra-inguinal venous bypass grafts compared to ASA. These recommendations are valid for above as well as below knee bypasses. The suggested optimal oral anticoagulation intensity to prevent secondary ischaemic and hemorrhagic events is an international normalized ratio (INR) of 3.0–4.0.[22]

In our survey, many long-term anticoagulation regimens are not in keeping with recommended treatment strategies. For above knee venous femoro-popliteal bypasses, 50% of all respondents use ASA alone and, therefore, do not comply with level I evidence. This therapeutic regimen may lead to early graft occlusion compared to vitamin K antagonists for venous bypasses. Moreover, 50% of all respondents routinely use vitamin K antagonists for prosthetic below knee femoro-popliteal bypasses. This may not only lead to increased incidences of early bypass failure compared to antiplatelet therapy in this patient group, but also to the possibility of 23 major bleeding episodes per 1000 patients annually.[16] Furthermore, only about 50% of INR readings are in the desired range, even under study conditions in dedicated anticoagulant clinics.[22] Therefore, half of the patients with prosthetic grafts are not optimally treated and at an increased risk of bleeding complications, and half of the patients with venous grafts are at increased risk of bypass occlusion and hence limb ischaemia.

Optimal antithrombotic strategies during and after vascular surgery are still under debate. They vary with the type of surgery, the use of grafts, and the clinical situation of patients. Obviously, the preference of antithrombotic therapies does vary internationally due to the presence or absence of dedicated anticoagulation clinics and also financial implications. This applies specially to clopidogrel, a well tolerated drug with minor superior beneficial effect compared to ASA. The most striking inconsistency for long-term postoperative anticoagulation is after infra-inguinal bypass surgery. Even though randomised controlled trials do exist for this specific issue, more than half of the replying institutions do not comply in some point with the evidence gained in these trials. However, clinical decision making of adequate antithrombotic therapy in peripheral arterial disease is demanding. This is also reflected by the organisation of the Peripheral Arterial Diseases Antiplatelet Consensus Group, who recently published guidelines for the use of antiplatelet agents.[23] In this light, Vascular Surgical Societies should be encouraged to define recommendations on antiplatelet therapy and anticoagulation for different vascular interventions.

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